Connective Tissue Disease

1. lupus Erythematus → 1
2. Chronic Discoid → 2
3. lupus panniculitis
   Tumidus
   chilblain lupus
   → 5
4. SubacuteCLE → 6
5. Acute LE SLE → 7
6. Neonatal LE → 13
7. late onset LE → 14
8. Scleroderma → 15
   Morphea
9. pseudosclerodema
   Systemic Sclerosis
   → 18
10. Esinophilic Fasciitis
    Eosinophilia-myalgia $
    Nephrogenic systemic
    Fibrosis
    → 24
    Stiff Skin syndrome → 25
11. Raynauds phenomenon → 26
12. Dermatomyositis → 27
13. Mixed CTD → 31
14. Antiphospholipid syndrome → 32
15. Relapsing polychonditis → 34
    SJogran Syndrome
16. تجميعات 35, 36
17. حالات مقارنة
    - Scleroderma - Scleredema
    - Scleroderma - pseudosclerodema
    - DLE - SCLE
18. اصبغات

Amylee

Autoimmune Connective Tissue Disease

①-: Lupus Erythematous :-

classification:

① Chronic Cutaneous LE CCLE

↳ chronic - Benign - No systemic

1- **D**iscoid LE (DLE)
- Localized (head - neck)
- widspread - Disseminated
- Hypertrophic

2- Lupus Erythematosus **T**umidus (LET)

3- Lupus **panniculitis**

4- **Chilblain** Lupus

* -ve Serology except :-
+ve **ANA**s Low titrs

* > Female

* ↑ HLA-B7 ↑-B8

② Subacute Cutaneous SCLE

1- photosenstive - Nonscarring ← annular, polycyclic, psoriasiform

2- mild **S**ystemic 50%.
mainly arthritis, rarely Renal

3- neonatal LE

4- C2 deficiency LE

* +ve Serology → +ve anti-RO 70%
+ve anti La

* -ve anti**n**DNA, anti-Sm - anti-RNP

* > Female

* ↑ HLA-B8 ↑ HLA-DR3

③ Acute Cutaneous SLE

1- Specific **S**kin lesion

2- Sever **multisystem** è Renal

* +ve anti nDNA, anti-Sm

* +Ve ANAs

* > Female

* Low Complement

④ Mixed Connective Tissue MCTD

⑤ Drug Induced

+ve n RNP antibodies
+ve anti-Histone antibodies

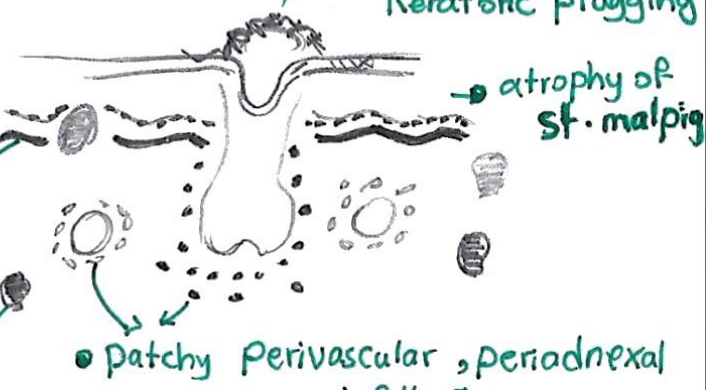
Chronic Cutaneous LE

① Discoid Lupus Erythematous → 5% of DLE → SLE

① Epidemiology:

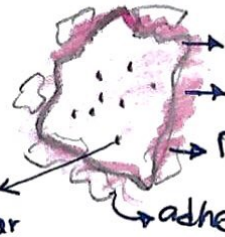
* **Age:** any age
  20-40
  ♀ Female
  ↑ HLA B7 - B8
* **PF:**
  - Trauma
  - Infection
  - Stress
  - Sun Burn
  - Drugs (griseofulvin)
* **Exacerbating F:**
  - Sunlight 70%
  - Cold
  - pre-menstrual

③ Histopathology:



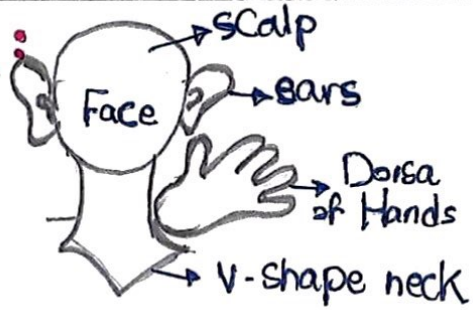
- Hyperkeratosis & Keratotic plugging
- atrophy of st. malpig
- Hydropic Degeneration of Basal cells
- Thickening of Basment membrane (Diagnostic)
- patchy perivascular, periadnexal lymphocytic infiltrate
- Edema
- Vasodilation
- extravasation of → Erythrocytes, Colloid Bodies in upper dermis
- pigmentary incontinence

② Clinical:



- well defined
- erythematous
- Discoid plaques
- adherent Scales → Follicular plugging (solidified plugs & Dilated pilosebaseous Canal "carpet tack" sign)

* **Site:**



* **Healing:-**

Thin-white atrophic Non-Contractile Scar & Slight Rise Hyperpigmented Border

- Mucous Membrane 3%
- Nail + eyes → Conjunctival Redness, Ectropion may occur

5 diseases بتجميعة Patchy Dermal infiltrate :

① Lymphocytic **Lymphoma**
- ATypical lymphocytes
- tightly packed
- interstial distribution "Indian filling"
- Not surrounding pilosbeacous unit

② **Lymphocytoma Cutis** :
- heavier infiltrate
- separated from Epidermis By narrow **GrenZ** Zone of normal Collagen
- mgy Be interstial distribution
- large paler lymphocytes arranged in lymphoid follicles

③ lymphocytic infiltration of **Jessner** :-
- perivascular - peri-appendageal patchy lymphocytic infiltrate
- NO Follicular arrangment

④ polymorphus light Eruption : plaque
- prominant Band of papillary Dermal edema
- infiltrate more intense in superficial

Causes of بتجميعة Hydropic Degeneration of Basal Cells :

1- LE
2- LP
3- Dermatomyositis
4- poikiloderma Vasculare atrophicans (PVA)
5- Erythema dyschromicum perstans
6- lichen sclerosus et atrophicus

Causes of بتجميعة Pigmentary incontinence :

كل اللي فوق
+- Fixed Drug Eruption FDE
- incontinenta pigmenti

where to find Colloid Bodies ; what is

1- LP
2- poikiloderma
3- FDE
4- lichenoid Keratosis
5- GVHD

→ Dermatosis with Damage to Basilar Keratinocytes

- large - Apoptotic - Keratinocytes
- Round - ovoid - Homogenous Eosinophilic Structure

④ Clinical Varieties:

1- **Localized** :- head + neck

2- **Generalized** . Disseminated :
- above + Below neck

3- **Hypertrophic (verrucous)** :-
- Non-pruritic
- papulo-nodular lesion
- arm - Hand - nose - ears

4- palmoplantar erosive .

5- papular :-
- pruritic
- umblicated papules
- on the Back
- Result: acneform Hypertrophic follicular scars

6- Rosacea-like :-
- Easy Flushing
- Diffuse erythema
- Reddish nodules
- No pustules
- nose - cheek - forhead - chin

7- Annular Atrophic

8- Telangiectatic
- peristant Reticulate Telangectasia

9- LE gyratum Repens :
- migratory gyrate annular Erythema

* ut is Rowel's Syndrome ?

- any ptn è DLE or SLE may Develop Erythema multiforme-like lesions
- on Face - neck - chest
- Lasting → Few Days

⑤ DIF:

- Diffuse irregular Band of IgG - C_3 [lupus Ban
  at DermoEpidemal Junction DEJ
  Below Lamina Densa
  in involved skin (90%)
- Not in uninvolved skin

⑥ Labs:

1/4 è + ANA (Low titr)

5-10% è DLE may Develop SLE

	② Lupus panniculitis	③ Lupus Tumidus	④ Chilblain lupus
lesion	- Firm - Asymptomatic - SC nodules - in DLE + SLE - normal overlying skin - healing: Cup shape depression	- Induration + Erythema - No Scale or Follicular plugging - lesion tend to : Resolve without Scarring or atrophy	- Red - Dusky - purple papules + plaques -
site	• Face • Breast • Bullocks • thigh • upper arm • upper Trunk 	• Face most common , may Be Trunk • DD: 1- Urticarial plaques in lupus ptns, But in tumidus are fixed 2- Jessner's lymphocytic infiltrate : Very closely Related or one and the same	• Toes - fingers • nose - elbo Knees - Lower legs 
HP	→ majority in Sub cut. tissue → predominantly Lobular lymphohistiocytic panniculitis → Vessel wall → Thickening → Perivascular inflammatory infiltrate → although all these → Lupus panniculitis Don't Represent True Vasculitis	- Epidermis → Uninvolved - intense Dermal inflammatory infiltrate - Marked deposition of Mucin	• exacerbated By : moist Cold Climates • the lesion Represent : Concurrence of ordinary Chilblains è lupus • with Time : The lesion may Develop gross or microscopic
DIF	→ immunoReactant around Dermal Vessels → S.C Fat → Difficult to examin By DIF	→ Non specific finding D:t Low prevalence of immunoglobulin deposition within the Cut. finding	

Subacute Cutaneous LE

→ persistent & intermittent flares
→ 50% will meet criteria of SLE (OR)

6

① Epidemiology:

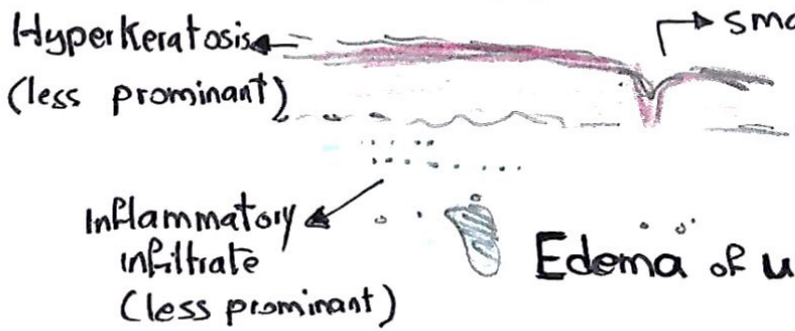
> Female
↑ HLA-B8
HLA-DR3

② Clinical:

1- prominant photosenstive Cut. lesions
- non-scaring
- papulosquamous OR Annular
- polycyclic lesion
- site: above the waist
- heal: grey white Hyperpigmentation
- Diffuse Non-scaring alopecia
- photosenstivity 50% of ptn

2- Mild Systemic lesion
→ 50% è criteria of SLE
→ Mainly: Arthritis
→ Rare: Renal
→ May occur: Interstitial Lung disease

③ Histopathology:



④ Serology:

1- lupus Band test → +Ve in 60% of lesions
25% of normal skin

2- FANA → Homogenous type 60-80% of ptn

3- Anti-nDNA, Anti-Sm, Anti-nRNA
AntiCardiolipin antibodies → Rare

4- Anti-RO antibodies → 80%
Anti-La antibodies → 30%

⑤ Drug-induced SCLE:

Thaizides (mostly) • D-pencilamin • Diltiazem
Sulfonylureas • Aldacton • Naproxen • Grisofulvin

Acute Cutaneous LE

Systemic lupus erythematosus SLE

① Epidemiology:

- → 20 - 40
- → > Female
- → African American women:
  - 4 folds >
  - High frequency of: nephritis, pneumonitis, Discoid lesions
  - Lower frequency of photosensitivity
  - earlier age
  - Higher mortality Rate

② Pathogenesis:

Genetic

- ↑ HLA-DR3 in neonatal LE mothers
- Ro +ve ptns
- older ptn SLE
- ↑ HLA-B8, DQ23 DRw52 in NLE mothers
- ↑ HLA-DR2
- anti-nDNA ptns

Immunologic

↳ T cell-defect:
- Suppressor cell
- Deregulation allow B-cell To over produce the immunoglobulin

↳ Try - B cell defect:
There's over-production of immunoglobulin

Environmental Factors

1- viral + Bacterial DNA + lipopolysaccharides

2- UV radiation →
- initiation + exacabation of inflammation
- trigger Cytokine + chemokine production

- activation of Dendritic cells
- Relase of interferon
- Production of chemokine
- Activation of T-cells

- initiating Immune Response
- The endpoint of Complex Cascade?

③ Histopathology of Cutaneous manifistations:

1- Hydropic Degeneration of Basal Cells
2- edema
3- extravasation of RBCs in upper Dermis
4- Fibrinoid Degeneration of CT of Dermis + wall of Bl vessels
5- Focal Mucoid Degeneration
6- lymphocytic infiltrate in subcutaneous Fat

* Hematoxylin Bodies: only on Autopsy

Biologic inhibitors/blockers of tumor necrosis factor-α

Induce formation of ANA & anti ds-DNA without clinical LE

Induce LE that differs from typical drug induced LE in

Skin manifestations, including malar rash, SCLE, DLE, photosensitivity & purpura, are prominent

ANA & anti-dsDNA antibodies are predominant, not antihistone antibodies

	Drug-induced SLE	Drug-induced SCLE
Skin lesions	Rare	SCLE or gyrate erythema
Serositis	Common	Occasional
Serology	Anti-histone Abs	Anti-Ro Abs
Drug	Hydralazine, procainamide, chlorpromazine, INH, quinidine, practolol, d-penicillamine, PUVA, minocycline.	Hydrochlorothiazide, terbinafine, diltiazem, ACEI, NSAIDs, griseofulvin, antihistamines, IFN, PUVA, TNF-α.

③ Cutaneous Manifistations:

Specific Skin lesion

1-  Facial "Malar" Erythema
Resolve without scar
over malar eminences
Spare NasoLabial Folds

2- Erythema on V-shape of Neck - Back of Hands
Shoulders
extensors of arms

3- photosensitivity Dermatitis

4- Bullous lesions:

- Bullous eruption of SLE
  - Dif → separation of DEJ
  - Dif → antibodies to Type VII collagen
  - clinically Resemble:
    - BP
    - EBA
  - Histopathology Resemble:- EBA / DH / BP
- Bullous or Crusted lesion
  - Result of intensity of Basal Cell Damage
  - in lesion of - ACLE / SCLE
- Dramatic Acute eruption
  - Similar to :→ Erythema Multiforme OR Toxic Epidemal Necrolysis TEN

Non-Specific - Connective tissue Disease Related skin lesions:

Vascular lesion (50-70%) → indicate Circulating immune complex Disease

1- periangual Telangectasia
2- Dermal vasculitis
3- Thrombophelebitis
4- Raynaud's phenamenon
10- atrophe Blanche
5- livedo Reticularis
6- Digital ulcers
7- Urticarial Vasculitis
8- peripheral gangrene
9- "Degos-like" infarct

Alopecia 40-60% :

- Frontal
- short Broken-off Hairs "Lupus Hair"
- OR Diffuse Non-Scarring

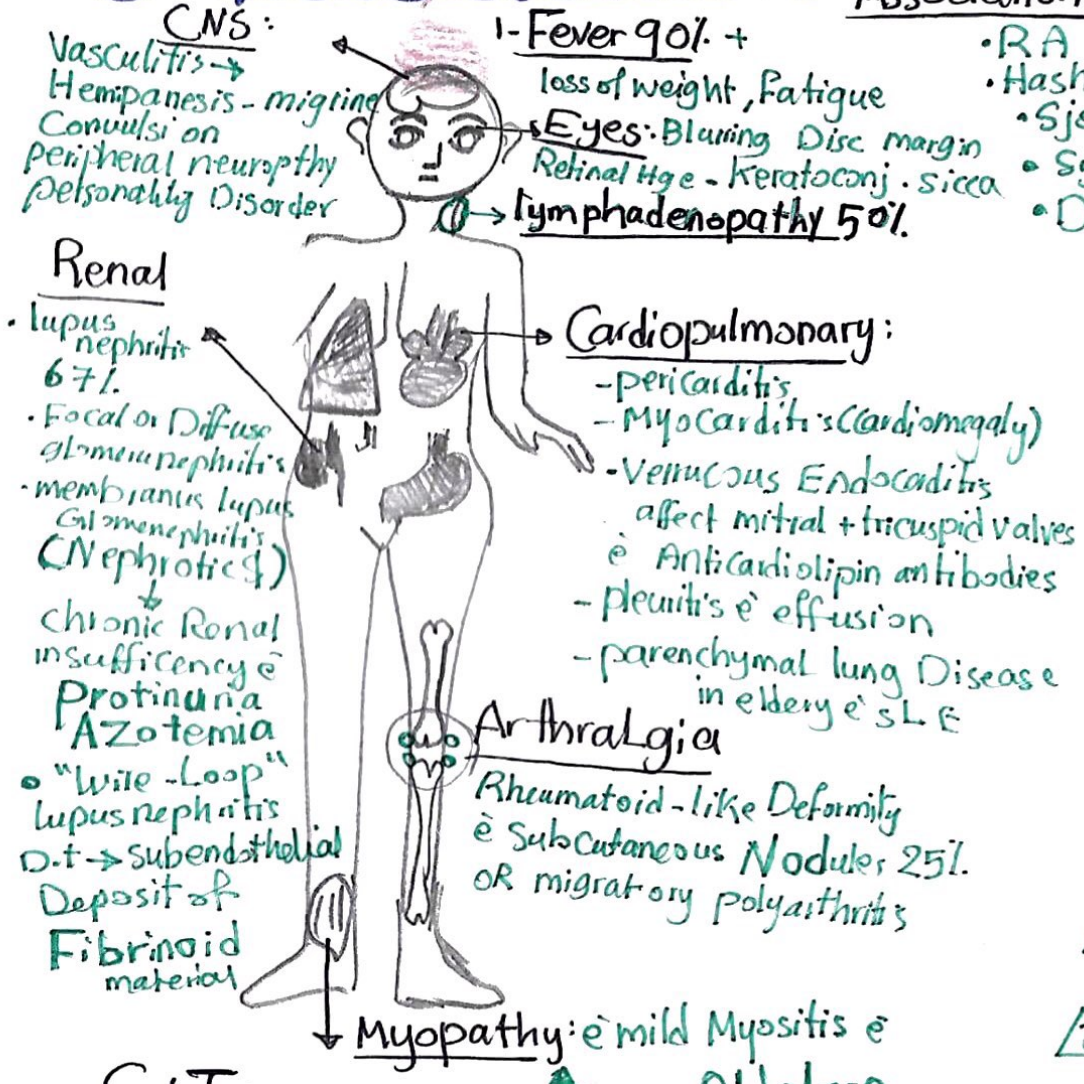
Calcinosis Cutis
Rare

Mucous Membrane:

- Hge
- erosions
- shallow ulceration
- gingivitis
- Erythema
- petechiae
- Erosions in hard palate

Pigmentary Abnormalities
Sclerodactyly - Urticaria

④ Systemic manifistations:



CNS:
Vasculitis →
Hemipanesis - migrine
Convulsion
peripheral neuropthy
Personality Disorder

1- Fever 90% +
loss of weight, Fatigue

Eyes: Blurring Disc margin
Retinal Hge - Keratoconj. sicca

→ lymphadenopathy 50%

Renal
- lupus nephritis 67%
- Focal or Diffuse glomerunephritis
- membranus lupus Glomerunephritis (Nephrotic↓)
  ↓
  chronic Renal insufficency è Protinuria Azotemia
- "Wile-Loop" lupus nephritis D.t → subendothelial Deposit of Fibrinoid material

Cardiopulmonary:
- pericarditis
- Myocarditis (Cardiomegaly)
- Verrucous Endocarditis affect mitral + tricuspid valves è Anticardiolipin antibodies
- pleuritis è effusion
- parenchymal lung Disease in eldery è SLE

Arthralgia
Rheumatoid-like Deformity
è Subcutaneous Nodules 25%
OR migratory polyarthritis

Myopathy: è mild Myositis è ↑serum Aldolase

GIT:-
Nausea - vomiting - Diarrhia
Loss of esophgeal motility • Splenomgaly
Ulcerative colitis

Other Associations
- RA
- Hashimsto thyroiditis
- Sjogren's Syndrome
- Systemic Scleroderma
- Dermatomyositis

⑤ SLE è pregnancy:
- Pregnancy has No effect on SLE
- Risk of intrauterine Death ↑↑ è anticardiolipin antibodies

⑥ Drug-induced lupus:
① Hydralazine - procainamide - Isoniazide
- produce LE-like manifistation
- rare Cutaneous or Renal manifistation
- Serology → -ve anti-nDNA Abs
  → +ve ANA, anti-histone Abs
- withdrawal → all Disapear

② D-penicillamine:-
Differ in frequent of Cut, Renal manifist, anti-nD

③ Hydrochlorothiazide: - SCLE-like - anti-RO Abs

④ Minocydine:

⑤ Biologic inhibitors / Blockers of TNF-A
Etanercept . infliximab

⑦ Lab Finding:

1- Urine: Proteinurea, Cellular Casts, RBCs

2- Blood:
- Hemolytic anemia
- leukopenia
- lymphopenia
- Thrombocytopenia
- Circulating anticoagulants
- lupus anticoagulants

3- ESR: ↑↑
- +ve Comb's test
- Serum gammaglobulin ↑
- RF → may present

4- False +ve Wassermann Reaction :- > 6 months

5- Serum Complement:
Low level = Disease Activity

6- LE Cell test: → LE cell is a neutrophil which ingested Basophilic homogenous nuclear material from another leucocyte → Neutrophil form Rosette apperance around Degenerated nuclear material
- Specific Not Very Senstive
- anti-nucleohistone" → Cause in vitro lysis of nuclear material → easy phagocytosed By neutrophils

+ve non-lesional Lupus Band test
- Dermatomyositis
- Rheumatoid Arthritis
- Iry Biliary Cirhosis

7- Direct IF (lupus Band test) 10

- Antibody deposition at DEJ + around Hair Follicules
  - These Deposits are **Granular**
    Composed of → IgG, IgM
- Complement protien Deposition
- in SCLE → Granular deposit in Epidermis
  D.t anti-Ro autoantibodies deposit Directly within the skin
- +ve in 90% of Involved skin in DLE, SLE
- +ve in 78% of uninvolved skin in SLE
  - 78% of Sun exposed
  - 55% Sun unexposed
- Uninvolved skin of Sun exposed → Diagnostic to Diffrenilate SLE from DLE
- Uninvolved skin Sun unexposed skin → Prognostic purpose → to find the Correlation Between lupus Band in uninvolved sun protected skin and Severity of Renal affection

8- Fluorescent ANA test : FANA

- +ve in 80%
- Not Diagnostic of CTD
  - may seen also in → old individuals, pregnancy, other autoimmune Disease
- its Screening Test → to Rule-in / Rule out LE
- Using MOUSE liver → Substrate
  - 2 Types of assays:
    - IIF → use Hep-2 epithelial Carcinoma Cells as substrate
    - ELISA → ↓ Cost (more popular)
- 5 patterns of ANA:

ANA	Antigen	Diagnosis	prognosis
peripheral	nDNA	SLE	poor
Homogenous	Histone	Drug-induced LE	Good
	nDNA	SLE	poor
Nucleolar	Nucelear RNA	PSS, SLE	poor
Centromere	Kinetochore	CREST	Good
Speckled	ENA		
	SM	SLE	poor
	RNP	MCTD	Good

- ANA titer: indicate Amount of serum Abs
  - → the higher the titer → the more Significant The test
  - → Low titer → Seen in healthy individuals
  - → ANA -ve SLE → Rare
    - ↳ present: photosensitivity, SCLE lesions, anti-Ro +ve
  - → ANA titre < 160 → little clinical utility

✱ Serological markers ✱

- Abs against Nuclear Constitutents:
  - -DNA
  - -Sn-RNP
  - -Sm
  - -nRNP
  - -La (ss-B)
- Abs against Cytoplasmic Constituents:
  - -Sc RNP
  - -Ro (ss-A)

9- DNA Abs:

Native DNA Abs
= Double stranded DNA
ds-DNA Abs
n DNA

- Highly specific for SLE
- 60% of ptn è active SLE
- Associated è Severe nephritis
- measured By:
Radioimunoassay
ELISA
IIF

Single Stranded DNA
SS-DNA

- non-specific (may present in other CTD) and in DLE
- 60% of ptn
- presence of SS-DNA → Serological link Between ptns è Cut Disease and those è more Classic SCLE

10- Abs to Extractable Nuclear Antigen (ENA)

12

Anti-Sm

- Resistant to Ribonuclease enzyme
- Highly specific for SLE
- only in 20%
- associated è ↑ Renal affection + CNS disease

Anti-nuclear Ribonucleoprotien nRNP-Abs

- Sensitive to Ribonuclease enzyme
- Commonly present in ptn è previously Diagnosed as MCTD
- Ptn è only n RNP Abs have Low prevalance of Renal affection compared è n DNA +ve ptns

La Abs

- Occur in 10% of ptn è SLE
- associated è Ro Abs

11- Histone antibodies:

- Present in 30% of Idiopathic SCLE
in 90% of Drug-induced LE
as: Hydralazine
procainamide
Isoniazide

12- Anti Cytoplasmic Abs

Ro: cytoplasmic glycoprotien
La: cytoplasmic RNA protien

- Present in 25% of ptn è LE
- include:
  - SCLE → 80%
  - Neonatal LE → 100%
  - C2 deficiency SLE → 75%
  - Oriental LE → 60%
  - ANA-ve LE → 90%
  - Late onset LE → 75%
  - Sjogren $ 40%

Autoantibodies associated with lupus erythematosus**

HL

Target	Median prevalence*	Molecular specificity	Clinical associations
High specificity for SLE			
dsDNA†	60%	Double-stranded (native) DNA.	LE nephritis & monitoring activity of nephritis.
Sm	10-30% of Caucasians; 30-40% of Asians & African-Americans	Splicesome RNP (ribonucleoprotein particles involved in splicing pre-mRNA).	
rRNP	7-15%; 40% of Asians	Ribosomal P proteins (proteins involved in ribosome function).	Neuropsychiatric LE.
Low specificity for SLE			
ANA (most common IF patterns: homogeneous, peripheral)	99%		
ssDNA	70%	Denatured DNA	Possible risk for SLE in DLE patients; also seen in RA, DM/PM, MCTD, SSc, SjS, morphea.
C1q	60%	C1q component of complement.	Severe SLE, hypocomplementemic urticarial vasculitis syndrome.
PCNA	50%	A component of multiprotein complexes involved in cell proliferation.	-
U1RNP	50%	Splicesome RNP	Overlapping features with other AI-CTDs; MCTD (100%).
Ro/SS-A	50%	hYRNP (quality control function for misfolded RNA molecules).	SCLE (75-90%), neonatal LE/congenital heart block (99%), SCLE-SjS overlap, primary SjS (70%); associated with vasculitis.
La/SS-B	20%	hYRNP	SCLE (30-40%), SCLE-SjS overlap, primary SjS (40%); occurs in conjunction with Ro/SS-A.
Cardiolipin	50%	Cardiolipin, a negatively charged phospholipid.	Recurrent spontaneous abortions, thrombocytopenia, & hypercoagulable state in SLE (cutaneous manifestations include livedo reticularis, leg ulcers, acral infarction/ulceration, hemorrhagic cutaneous necrosis); similar associations in primary antiphospholipid antibody syndrome; clinical manifestations have strongest association with IgG class of anticardiolipin.
β2 glycoprotein I	25%	An important cofactor for cardiolipin in cardiolipin aAb assays.	Relatively high risk of thrombosis in SLE & primary antiphospholipid antibody syndrome.
Histones	40%	Histones	Drug-induced SLE; also RA, SLE & SSc with pulmonary fibrosis (in conjunction with other aAb).
Rheumatoid factor	25%	Fc portion of IgG	Nonspecific
Ku	10%	DNA end-binding repair protein complex.	Overlap with other AI-CTDs such as DM/PM, SSc.
Alpha-fodrin	10%	An actin-binding protein at the periphery of chromaffin cells that may be involved in secretion.	SjS

** Based on most common assay techniques currently employed in clinical immunology laboratories.*

Neonatal LE (NLE)

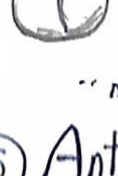
- Occur mainly in: Female infants of mothers who Have or will Develop CTD

periorbital "owel-eye" "eye-mask" scalp

Annular Erythematous lesions

Extremity

- the infant Develop:
  - SCLE-like lesion
  - Develop within
    1. 2 months
       - Improve in 4-6m
       - Crusted lesion in male ptns
    2. photosensitivity
    3. Tranisent → Thrombocytopenia
       → Cholestatic hepatitis
    4. Complete Congenital heart Disease Block "permenant"
       "may occurr in absence of Skin Disease"

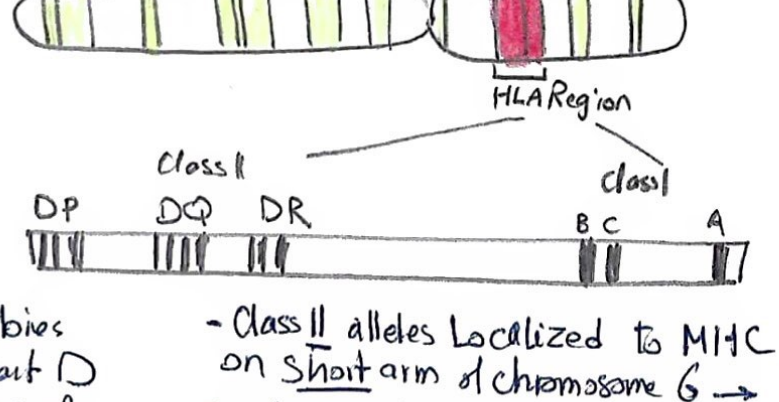


mothers of Babies è Congenital heart D have 1:3 chance of Developing SLE

    5. Anti-Ro Abs in < infants / mothers
       "Serological maiker"
       Disappear By 4-6 mnths of age
    6. ↑ prevalence of HLA-DR3, B8 in mothers

- Lab + Immunological study:
  - children è Cutaneous NLE → Should evaluated For → Hematologic + Hepatic + Cardiac involument

chromosome 6



- Class II alleles Localized to MHC on short arm of chromosome 6 → control anti-RO, anti-La auto antibodies
- ↑↑ Frequency of HLA-DR2 DR3 è anti-RO Abs Response
- There is strong interRelation Beleen all phenotypically diffrent anti-RO Abs +ve women ↓ all have Risk of giving Birth to infant è NLE

To sum-up, antibodies can give a clue to the diagnosis and prognosis of LE patients

Antibody	Features	Prognosis
nDNA	Severe nephritis, specific for active SLE	Poor
ssDNA	Non-specific for SLE, found in other CT diseases, & may be DLE (suggesting possible disease progression)	Good
Sm	Specific for SLE, ↑ incidence of renal & ? CNS dis.	? Poor
nRNP	Raynaud's phenomenon, sclerodactyly, arthralgia, pulmonary disease, eosophageal dysmotility & rare renal affection "MCTD"	Good
Ro & La	(photosensitivity, mild renal disease): SCLE, oriental LE, ANA –ve SLE, neonatal LE, C2 deficiency SLE, Sjogren's syndrome & late-onset LE	Good
Histones	Drug-induced SLE	Good

Classification of LE spectrum

	Leading Abs	Features	Prognosis
Mild	Ro "SS-A"	SCLE, ANA –ve LE, neonatal LE, C2-deficient LE	Good
Moderate	Sm or nRNP	MCTD	Good
Severe	nDNA	SLE	Poor

Late onset LE

- **ocur in**: eldery > 50 years
- **chich By**:
  - ↑ incidence of
    - ↳ Neuropsychiatric + pulmonary manifestations
  - ↓ Frequency of **Renal** Disease
  - photosenstive lupus skin lesion
  - SCLE
  - Cutaneous Vasculitis
  - Frequent **Sjogren's** $
  - ↑ incidence of Anti-**Ro** Abs 75%
  - ↑ incidence of **HLA DR3**

Q: features associated è anti-RO antibodies +ve Sjogren's $:

→ SS < 1ry / 2ry

→ in associated è LE, DM, sclerodema, MCTD

→ clinical: Vasculitis
- Anemia
- Salivary gland enlarge
- lymphadenopathy
- Thrombocytopenia
- Hypergammaglobulinemia

Treatment of lupus

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① Local:

1- **Sun** protection: UVB Sunscreen
2- Topical **Corticosteroids**: **Betamethasone** di proprionate, **Triamcinolone** acetonide I. lesional 3-4 mg/mL
3-
3- Topical **Calcineurine inhibitors**
4- Topical **Retinoids**

② Systemic antimalarial (Gold standard)

1- **Hydroxychloroquine** → 6.5 mg/kg/day
2- **Chloroquine** → 3.5-4 mg/kg/day
3- **Quinacrine** → 100 mg po qd
4- Combination of Hydroxycholroquine or chloroquine

③ Systemic antimalarial-Resistant

1- **Retinoids** - (acitretin - Isotretinoin)
2- **Thalidomide**: Highly effective But Teratogenic Neurotoxic
   - ↳ used only in → men
   - ↳ post menopausal women
3- **Dapsone**: 100 mg/day
   - ↳ For Bullous eruption LE
4- **Imunosuppressive agents**: → Azathioprine, ↳ Mycophenolate mofetil
5- **Sulfasalazine**:
6- **Clofazimine**: 100-300 mg/day
7- **Systemic Corticosteroids**
8- Rituximab, anti-IL-6 Ab, anti-IL-10 Abs

Scleroderma

1-D.F:
- Both: Systemic Sclerosis + Cutaneous Sclerosis
- e.g: morphea, Linear scleroderma

① Morphea: Localized Scleroderma

- D.F: Fibrosing Condition limited to: Skin + S.C tissue, underlying Bone, Rarely CNS if present at face or head
- to Difrentiated From SS → 1- absence of Sclerodactyly, 2- Raynaud Phenomen, 3- Nail fold Capillary changes, 4- Organ involvement

Clinical:

① **Plaque**
- Round or Oval
- Indurated ivory Smooth surface
- Violaceous Lilac Border
- lesion improve within 3-5 yrs è Residual Hyperpigmentation

② **Guttate:**
- Resembling Lsea lichen sclerosis et atrophicus But without Hyperkeratosis OR follicular plugging

③ **Linear Morphea**
- ① En coup de Sabre: linear depressed groove on frontoparital Region → extend to Scalp → "Linear alopecia"
- ② progressive HemiFacial atrophy: parry Romberg Syndrome

Epidemiology:
- Rare, > Female
- 20-40 yrs
- Some Cases Caused By: Borrelia Burgdorferi è manifistations of Lyme's Disease → who live or travel to Endemic area → OR History of Tick Bite
- Mainly Tested For Abs to Spirochete

④ **Generalized Morphea**
widspread è out systemic involvment

⑤ **Deep morphea**
Diffuse induration of Tissues → extend from Deep Dermis to S.C Tissue + Fascia

⑥ **Disabling pansclerotic of children**

⋆ Classification:

(A) Localized Cutaneous Sclerosis (Localized sclerodema) (morphea)

1- Plaque:
- plaque
- Guttate
- Atrophodema of pasini + peiini
- Keloid morphea → nodular
  → lichen sclerosis et atrophicus

2- Linear:
- linear
- En coup de sabre
- progressive hemifacial atrophy

3- Generalized:

4- Bullous.

5- Deep:
- S.C
- Eosinophilic fasciitis
- morphea profunda
- Disabling pansclerotic

6- as a Componant of Overlap Syndrome:
- MCTD
- Sclerodematomyositis

(B) Pseudosclerodemas

(C) Systemic Sclerosis (SS)

limited Cutaneous
- acrosclerosis
- CREST $

Diffuse Cutaneous

- Disabling aggressive mutilating form
  - affecting **All** tissues to **Bone**
- Rare
- predisposes ptn to **SCC** of skin

✱ Most Common presention:

- **Plaque** → more in **Adults**
- **Linear** → more in **Children**

presented Fibrosis of underlying Tissue → ↑ mabidity

✱ Systemic:

- most common extraCut is **Arthralgia**
- **CNS Fibrosis** → most common in children è head + neck involument
- Should have Regular Ophthalmic examination to monitor Asymptomatic involvment → irreversible Damage.

✱ Histopathology:

Early inflammatory stage

- marked lymphocytic infiltrate (H) Lower Dermis + S.C fat
- Large area replaced By: newly formed **collagen** fibers
- Thickened Trabeculate of **S.C Fat**
- ↑↑ number of **Mast cells**

Late Sclerotic stage

- **Disappear** of inflammatory infiltrate
- **Collagen** consist of Thick, closely packed, Hyalinized Bundles few fibroblasts
- **eccrine glands** → atrophic, tightly "Bound Down" By the newly formed collagen

✱ Laboratory:

1. Investigations of SS → -ve
2. **Eosinophilia**
3. +ve **ANA** in 40% of **Linear** morphea
4. Anti-ssDNA Abs → +ve 70% of **Generalized**
   53% of **Linear**
   25% of **Localized**
5. Serum procollagen type 1 - **Carboxy Terminal** Peptide → 30% in Localized, more in Generalized

✱ Treatment of Morphea

limited plaque

Topical Tacrolimus

↓ No Response after 8 wks

- lesion limited → Phototherapy (NB-UVB - UVA - UVA-1)
- ✱ Topical imiquimod
- ✱ Calcipotriol + Betamethasone dipropionate

linear morphea involving Face - crossing joints

Methotrexate + Systemic Steroids

↓ No Response after 8 wks

- phototherapy (UVA - UVA1 - NB-UVB)
- ✱ Change Therapy to Mycophenolate Mofetil

Generalized Morphea without joint Contracture

Phototherapy (UVA1 - UVA - NB UVB)

↓ No Response after 8 wks

Methotrexate + Systemic Steroids

↓ No Response after 8 wks

Change therapy to Mycophenolate Mofetil

✱ NB-UVB → effective as Low Dose UVA-1

✱ Topical Tacrolimus → effective in the For Activeplaque Morphea

✱ Methotrexate & systemic Steroids and UVA-1 → the Most evidence of efficacy in the of Severe Morphea

② Pseudosclerodermas

1-D.f: many Diseases or Environmental Factors → induce Scleroderma-like Changes

2-Causes:

- Genetic
  - Progeria
  - Rothmund-Thomson$
- Metabolic
  - PCT
  - Amyloidosis
  - POEMS$
  - Scleromyxidema
- paraneoplastic $
  - Carcinoid $
  - Bronchial Carcinoma
- CGVHD
- Acrodermatitis Chronica atrophicans
- Connective Tissue Diseases
  - SLE
  - DM
  - RA
- occupations + chemicals
  - Pesticides
  - Silicosis
  - Epoxy Resins
  - L-Tryptophan
- Iatrogenic
  - Bleomycin
  - INH

③ Systemic Sclerosis!

limited (Acrosclerosis)

- limited to → Hands, Forearm, Face
- with Disseminated Telangectasia
- Long History of Raynaud's phenomen
- C R E S T
  - C → Calcinosis
  - R → Raynad's
  - E → Esophgeal Dismotility
  - S → Sclerodactyly
  - T → Telangectasia

Diffuse

- involve Both Truncal & Acral areas
- without significant Telangectasia
- Short interval < 1 yr Between the onset of Raynauds phenomenons + Development of Skin changes

→ Diagnostic Criteria of SS:

Major	Minor
- Proximal Truncal Sclerosis	1- Sclerodactyly
	2- Digital pitting Scars
	3- Loss substance of Digital finger peds "pulp loss"
	4- Bibasilar pulmonary fibrosis

1 major + 2 minor = 97% Diagnosis

④ **Telangiectasia:** Face + Hands

⑤ **Calcinosis** Palmar aspect of Terminal phalanges

⑥ **Abnormal Nail Fold Capillary pattern**

⑦ **Ulceration above tip of fingers:**

→ Clinical manifistations:

Cutaneous

① **Skin Sclerosis**
- early edematous phase
- Sclerotic phase
- Late atrophic phase
- **Skin is**
  - Diffuse indurated
  - Smooth + Shiny
  - firm Bound to underlysing Structure
- **finger + Hands:**
  - swollen
  - Tumid
  - Can't fully extend
- **Face:**
  - Small
  - pinched nose
  - constricted mouth
  - Radial Furrows

② **Raynaud's phenomen**

③ **Hyper + Hypo pigmention**
- Diffusely
  - Salt - pepper reflecting perifolicular Hyperpigmention against Hypopigment Background

Systemic

- **lung:**
  - pulmonary fibrosis
  - palmonary Hypertension
  - Rt-side HF
- **Heart**
  - pericarditis
  - pericardial effusions
- **Kidney:**
  - proteinuria
  - azotemia
  - Hypertension
  - Sclerodemal Renal crisis
- **Musculo Skeletal**
  - Arthralgia
  - arthritis
  - Myositis
  - Contractures
- **GIT**
  - esophgeal Dysmotility
  - Dysmotility in small Bowel & Colon
  - Regurgitation
  - malabsorption
  - Peptic esophgitis

→ Cause of Death:

1- Renal Failure
2- Cardiac complications of malignant HTN
3- Because of use of ACEI Hf of Renal crisis

Renal Failure Now is Not the main Cause
Replaced By Pulmonary Disease

→ Systemic Sclerosis Sine Scleroderma:

1- Internal organ involument
2- Raynad's phenomenon
3- +ve Serology
4- No Cutaneous involument
5- ptns prognosis similar to that of ptns è limited SS

→ DIF:

- ve

→ D.D of SS:

	Diffuse	limited
- Onset	Abrupt	Gradual
- Skin Sclerosis	- Truncal . Acral - without significant Telangectasia	- limited to Hand, forearm, face - è Disseminated Telangectasia + Calcinosis
- Raynoud's	onset within 1yr of onset of Skin changes	- Long History
- Systemic affection	- Early onset of interstial Lung Disease Renal Failure, GIT, MI	- late onset : pulmonary HTN
- Nail Folds Capillary	- Dilation + Destruction	Dilation without Dropouts
- Auto Abs	- SCL-70 (anti-topoisomerase)	- AntiCentromere Abs +ve
- prognosis	- Poor	- Good

→ Serology: By: indirect Immunofluorescence on Hep-2 Cells

→ 3 ch.ch. patterns:

① Anticentromere Abs: (Speckled) in Limited Cut more in CREST
② SCL-70 (Diffuse fine Speckles) Diffuse Cut
③ Antinuclear Abs (speckled - Homogenous - clumpy)
limited, Scleroderma polymyositis overlaps, Diffuse

Autoantibodies associated with SSc & morphea (localized scleroderma)** HL

Target	SSc, all	SSc with diffuse cutaneous scleroderma	SSc with limited cutaneous scleroderma (also referred to as CREST syndrome)	Morphea (localized scleroderma)
ANA (most common IF patterns: speckled, nucleolar, centromere)	95%*			40%
Centromere (CENP-B)		30%	80% (pulmonary hypertension)	
Scl-70 (DNA topoisomerase I, which unwinds DNA)		60% (pulmonary fibrosis)	15%	
Fibrillin-1 (major component of microfibrils in the extracellular matrix)		5%	10%	30%
Histones	40%			35%†
Rheumatoid factor	25%			25%
ssDNA	10-30%			50% (may correlate with disease severity or activity; most prevalent in linear morphea)
Fibrillarin (U3RNP)	5%	Internal organ involvement		
PM-Scl	5%	Polymositis, SSc overlap		
RNA polymerases	5-20%	45% (aAb levels correlate positively with extent of skin involvement & renal disease)	6%	
Th/To RNP (mitochondrial enzyme) (associated with limited pulmonary fibrosis)		11%	19%	5%
Calpastatin‡	25%			
HMG (high mobility group); a non-histone nucleosomal protein		30%	40%	
MMP 1 & 3 (degrade ECM proteins; aAb prevents degradation)	52%	71%	33%	
PDGFR (platelet-derived growth factor receptor): expressed on fibroblasts§	16-100%§			

* Median prevalence using current assay techniques

→ Pathogenesis:

- Autoimmune process OR Unusual Reaction to chemical
- 3 pathways in Early Scleroderma

① Vascular alteration

1- Endothelial cell injury

proliferation of intimal cells
↓
Obliteration
↓
→ Ischemia + platelet Hyperaggregation
→ Relase of mediators
→ modulation of fibroplast functions

→ Altered permeability of Vessel wall → ↑ passage of Mononuclear cells into tissue

2- Surrounding Smooth muscle cells
→ altered production and Responsivve to Vasoconstrictive (cold - endothelin) and Vasodilatory (nitric oxide)

② Abnormal Immune Regulation

- presence of Autoantibodies against Nuclear + Cellular antigen
- ↑↑ T- helper cell activity

3- Raynaud's phenomen + Digital ulcers:

Caused By Reversible vasospasm OR Irreversible arterial Damage with intimal proliferation and luminal obstruction

4- Scleroderma Renal Crisis + Pulmonary artery Hypertension
↓
manifistation of Large Vessel Dysregulation

③ Disturbed Control of Collagen metabolism

- excessive Deposition of Collagen type III
  Proteoglycans
  fibronectin
  fibrillins
  Adhesion molecules
  ↓
  which Sequester Cytokines + growth factors

Cytokines of possible relevance to SS

Cytokine	Cell source	Actions	Correlation with SS
IL-2	TH1 subset.	• Capillary leaks. • ↑ T & B cell proliferation. • Monocyte activation.	• Extravasated fluid / edema. • Lymphocytic infiltrates.
IL-5	TH2 subset.	• B cell activation. • Eosinophil proliferation. • Mast cell proliferation.	• Autoantibody production. • Hypergammaglobulinemia. • Eosinophilia. • Increased mast cells.
TGF-β	T-cells, activated monocytes, platelets.	• Collagen synthesis. • Glycosaminoglycan synthesis. • ↓ Lymphocyte proliferation. • Angiogenesis.	• Increased sclerosis coincident with decreasing infiltrates. • Telangiectasia.
TNF	Activated monocytes.	• ↑ PGE2 synthesis. • ↑ Angiogenesis. • ↑ IFN synthesis. • ↑ Osteoclast activity. • ↓ Fat synthesis. • ↓ Proteoglycan synthesis. • ↓ Collagen synthesis.	• Loss of dermal & subcuticular substance. • Hyperpigmentation. • Telangiectasia. • Bone resorption.

IL = interleukin, TH = T-helper cell subset, TGF = transforming growth factor,

TNF = tumor necrosis factor, PG = prostaglandin, IFN = interferon

→ Molecular pathogenesis :-

1- morphea lesion → initiated By Vascular injury

2- Vascular injury → ↑↑ expression of adhesion molecules → inflammatory Cells recruit

3- The Recurit inflammatory Cells → ↑↑ production of Cytokines

4- The profibrotic Cytokines → ↑ Collagen production + ↓↓ Collagen Destruction → Result in overabundance of Collagen Deposition

→ Role of Mast Cells :

- ↑ number of Mast Cells in Early inflammatory stage
- 2ryto IL-5 Relased By :- activated T-helper Cells
- mast cell-derived proteases Cause endothelial Cytotoxicity

→ Fibrosis in scleroderma Result from the interplay Between :

Recruitment of lymphocytes + monocytes

1- T-cell activation → Relase of IL-2 , IL-5 TGF-β

2- B-Cell activation → anticentromere + SCL-70 Abs

3- Monocytes activation → Fibronectin , IL-1 , TGF-β TNF

4- CTGF → Connective Tissue growth Factor
- induced By TGF-β
- Responsible for mainenance of Collagen Synthesis

Activation of fibroblasts

- Selective population of fibroblasts (those Localized in Lower dermis) → Stimulated → enhanced Collagen Synthesis (Type I-III)
- This is D.t →
  - ↑ T-helper function → production of Collagen stimulatory lymphokines
  - Defective inhibitory FeedBack By amino-propeptides of Type I-III collagen

→ Treatment of SS :

1- **Steroids:** Topical / Intralesional / oral (if generalized)

2- **Penicillamine** (300 - 600 mg/day) + **pyridoxine** (20 mg/day)

3- **Potassium para-amino Benzoate** oraly

4- **PUVA • UVA-1 • Cyclosporine A • Plasmapheresis** Combined ← **Oral steroid**

5- **vit-D analogues** - oral \ Topical

6- **Oral Salazopyrin** (2 - 4 g/day)

7- **Physiotherapy**

8- **plastic surgery**

9- internal organ ttt

Renal Crisis :-

if elevated > 20 mmHg Systolic + > 10 mmHg Diastolic pressure

→ Renal crisis suspected

→ **ACEI** → Started

Esophageal involv :- → proton pump inhibitors

Pulmonary Disease :-

Interstitial lung Disease

- Cyclophasphamide
- Chlorambucil
- Cyclosporine
- Corticosteroids
- Mycophenolate Mofetil
- Azathioprine
- 5-Fluorouracil

pulmonary arterial HTN

→ Oral Vasoactive compounds :

1- Endothelin receptor antagonist
- Bosentan
- ambrisentan

2- phosphodiesterase type 5 inhibitors
- Sildenafil

3- prostacycline analogues
- iloprost (inhaled)
- treprostinil (s.c)

For pulmonary arterial HTN

10- Future :-

- anti-TGF-β Abs
- anti-CTGF therapy
- autologus stem cell transplant
- SCOT trial → Scleroderma Cyclophasphamide or Transplant

④ Eosinophilic Fascitis "Shulman $"

- D.F: Sclerodema-like Syndrome
  - è Distinct entity
- C/P: gradual OR sudden Onset:
  - Swelling - Stiffness of extremities
  - Asymmetric - Deeply indurated - Bound-Down plaques of skin + S.C
  - Site: extremities, forearm, Legs. Sparing Hand, Feet
  - Skin: puckered - cobble-stone appearance
  - Flexion contracture + limitation of movment
  - Raynaud + visceral change → Not present
- Lab Finding:
  1. Striking peripheral eosinophilia
  2. ↑ ESR
  3. Hypergammaglobulinemia
  4. Rare → aplastic anemia
     → Thrombocytopenia
  5. ↑ serum ALdoLase level
  6. Normal serum Creatine Kinase Level

⑤ Eosinophilia-Myalgia $

- Acute-Multisystem Disease-è peripheral Blood esinophilia + Sever Myalgia
- History of Recent intake of L-tryptophan

- Erythematous Macules, pruritic
- site: extremities, trunk
- è: edema-Hyperesthesia
- Resolve: within 2-4 wks
- Develop: progressive - Woody induration of skin, Hyperpigmention
  - Peau-d'orange
  - Diffuse Alopecia
- Spare: Face, Acral portion of Body
- Raynaud: Abscent
- Nail Fold abnormalities: Abscent
- extracut manifist:-
  1. Sever Myalgia
  2. Pulmonary: Cough, dyspnea
  3. Neurologic affection: peripheral + Central Neuropathy
  4. Arthralgia
  5. Cardiac
  6. GIT: Steatorrhea.

⑥ Nephrogenic Systemic Fibrosis

- exclusive in individuals è impaired Renal Function
- Dialysis Dependent chronic Renal Failure (2
- Following exposure to: gadolinium-Based Contrast-medum

- C/P: Ill-defined Thick-indurated plaques
- Symmetric.
- site: extremities Trunk
- Brawny Hyperpigmentio
- ± Joint Contracture

- histology: Dermal sclerosis ↑ CD34 + Cells

- tt: UVA-1 Restoration of Renal Function

Eosinophilic Fascitis

Histopathology:

- Dermal Sclerosis & Inflammation + Fibrosis of Fat + Deep Fascia
- Then they Thickened + infiltrated & → lymphocytes, → Plasma Cells, → Histocytes (esinophilis)

Tt: Systemic Steroids (40-60 mg/day)

OR Anti-Malarial agents

↓

- Improvement
- Spont. Remission may occur

Esinophilia - Myalagia §

Histopathology:

- Marked Thickening of Fascia
- Inflammatory infiltrate of Marked esinophilia → lymphocytes, → Plasma Cells, → Mast Cells

In Fascia, septa, S.C tissue + Deep Dermis

Tt: 1- Systemic Steroids

2- NSAIDs

3- Oral Isotretinoin (60 mg/day)

⑦ Stiff Skin Syndrome

25

- Rocks hard induration + Thickening of skin + S.C tissue
- Most in Buttocks, Thigh
- Chich: Sparing inguinal folds

↓

D.t Distrubance in the organization of collagen + glycosaminoglycans in extracellular matrix

Raynaud's phenomenon:

- **D.F:** Episodic Vasospasm of Digital arteries → white, Blue, Red Discoloration of fingers, 2ry to → Cold Stimuli

- **Types:**

	1ry	2ry
Sex	F:M 20:1	F:M 4:1
Age of onset	Pubeity	>25yr
Frequency of attacks	<5 per day	5-10+ per day
PF	Cold - emotional stres	Cold
Ischemic injury	Absent	present
Abnormal Capillaroscopy		>95%.
Antinuclear Abs	Absent / Low titer	90-95%.
Anti-SCL 70	Absent	20-30%.
in vivo platelate activation		>75%.
anti Centromere Abs		50-60%.

- **DD:**

✱ **Structural Vasculopathies**

↳ large + Medium size:
- Thoracic outlet Syndrome
- Takayasu's arteritis

↳ Small arteries + arterioles:
- Systemic Sclerosis, SLE, DM
- Cold injury - Vibration

✱ **Abnormal Blood elements:**
→ Cryoglobulinemia → Cryofibrinogenemia
→ Myeloproliferative Disorders.

✱ **Abnormal Vaso-motion:**
→ 1ry (idiopathic) Raynauds
→ Drug induced :- ergots, interferon, estrogen
→ Cyclosporine
→ Pheochromocytoma → Carcinoid S

- **Tt:** 1st line: avoid Cold + tobacco

2nd line: 1- VasoDilators: CCB, ARB, phosphodiesterase inhibitors
2- I.V prostaglandin E1: alprostadil
3- Nerve Blocks + sympathectomies
4- Antiplatelet agents :- Low Dose Aspirin
5- Topical preparations: ineffective

Dermatomyositis

- **D.F:** Rare Inflammatory Myopathy with chich Skin + Muscle weakness

***polymyositis**
Similar Disease **without** Skin lesion

***Amyopathic DM**
- Typical Cut. manifist of DM
- **without** clinical OR Laboratory Finding of muscle involv. for **at least** 2 yr after the onset of Rash

- **Etiology:**

1- Adult onset
- classic
- classic è Malignancy
- classic as a part of an overlaping CTD
- Amyopathic
- Hypomyopathic

2- Juvenile
- classic
- clinically Amyopathic
  - → Amyopathic
  - → Hypomyopathic

3- polymyositis 27
- Isolated
- Polymyositi as a part of overlappuig CTD
- associated è internal malignancy

4- Inclusion Body myositis

⑤ Drug precipitant
- D-pencillamine
- Hydroxyurea
- NSAIDs
- Cyclophosphamide

⑥ Malignancy association in adults

① Envirnmental
1- picorna virus – muscle + Capsid protien
2- E.coli
3- Echovirus infection in ptn è Hypogammaglobulinemia
4- Coxsackie virus-9
5- AIDS myositis

② Autoimmune
- è Autoimmune D
  - → Hashimoto's
  - → Graves D
  - → Myasthenia gravis
  - → Type1 DM
- Autoantibodies
  - → Antisynthetase Jo-1
  - → anti-translation-KJ
  - → anti-Mi-2

③ Genetically Determined aberrant Immune Response
Viral → as infectious agent
- → HLA-DR3+B8 (Juvenile DM)
- → HLA-DR52 (ptn è anti Jo-1 Abs)
- → HLA-DR7-DRW53 (ptn è anti Mi-2 Abs)

④ Cellular immunity
1- CD8 lymphocytes in [skin / muscle]
2- ↑ Ki-67 - P53 expression in Keratinocytes after UVB
3- ↑ CD40 expression in muscle cells
4- Fas ligand on T cells
Fas Receptor on muscle cells
5- ↓ CD54 (ICAM-1)
6- ↑ Expression of COX-1, COX-2, 5-LOX mRNA

- clinical Features:

Cutaneous

A) pathognomic

1- Gottron's papules:
- violeacous Flat-topped papules
- Dorsal interphalangeal - Elbow
- Metacorpophalangeal - knee Joints

2- Gottorn's Sign:
- Macular violaceous Erythema
- with or without edema

B) other signs

1- periungual telangectasia & Ragged Cuticle "Samitz sign"

2- Heliotrope Erythema
violeaceous & Slight edema in Face specially Periorbital, upper chest + arms

3- poikiloderma: shoulder- arms upper Back

4- S.C + periarticular Calcification
if excessive → Dystrophic Calcinosis Universalis

5- photosenstivity - fissured, scaly Hands = Mechanic 'Hands"
aquired Ichthyosis

Skeletal

→ Progressive Symmetrical weakness
→ later atrophy of proximal muscles of extremities
- Difficult walking - up stairs
- getting up from chair
- Combing Hair

→ involve pharyngeal + neck flexor
↓
Dysphagia - Fatigue

→ Involve Diaphragm
↓
Respiratory failure

C) Uncommon Skin Features:

→ erosions + ulcers
→ Holster sign (poikiloderma of lateral thigh)
→ Flagellate erythema
→ vesicoloBullous lesion
→ panniculitis
→ gingival Telangectasia
→ pustular eruption of Elbow + Knee
→ Lipoatrophy
→ Exfoliative Erythroderma

Systemic

Pulmonary
- in antisynthetase Syndrome
↓
Interstial lung Disease
(myositis + antisynthetase Abs)

Myocardial
major prognostic Factor for Death
- arrythymia
- CHF
- myocarditis

GIT
- Dysphagia
- esophgeal Dysmotility

Causes of Dysphagia in DM
→ Overlap & sclerodema
→ Cricopharyngeal muscle Dysfunction
↓
Difficult initiating Swallowing

Ocular
Conjunctival edema - Nystagmus

Arthralgia
Symmetrical

Serum autoantibodies in adult & juvenile dermatomyositis

Autoantibodies	Target antigen function	Clinical phenotype	Response to steroids
Anti-aminoacyl-tRNA synthetases (e.g. anti-Jo-1 'histidyl', anti-PL-7 'threonyl')	Intracytoplasmic protein synthesis	Antisynthetase syndrome.	Moderate
Anti-SRP	Protein translocation (anti-signal recognition particle).	Fulminant DM/PM, cardiac involvement.	Poor
Anti-Mi-2	Helicase-transcription (anti-helicase nuclear proteins).	Adult DM & juvenile DM (hallmark is cutaneous disease, milder muscle disease with good response to treatment).	Good
Anti-p155	Anti-transcriptional intermediary factor 1 gamma.	Clinically amyopathic DM; in adult-onset classic DM, increased risk of malignancy.	
Anti-p-140	Likely NXP-2-nuclear transcription, RNA metabolism	Juvenile DM with calcinosis.	
Anti-SAE	Post-translational modification	Adult DM; may present with clinically myopathic DM.	
Anti-CADM-140 (MDA5)	Innate immunity	Clinically amyopathic DM; rapidly progressive interstitial lung disease.	

Antiaminoacyl-tRNA synthetase antibodies & their associated antigens in polymyositis/dermatomyositis HL

Antibody	Antigen	Polymyositis/dermatomyositis patients with antibody (%)
Anti-Jo-1	Histidyl-tRNA synthetase	20
Anti-PL-7	Threonyl-tRNA synthetase	<3
Anti-PL-12	Alanyl-tRNA synthetase	<3
Anti-OJ	Isoleucyl-tRNA synthetase	<3
Anti-EJ	Glycyl-tRNA synthetase	<3

★ Juvenile Dermatomyositis ★

→ Resemble of Adult except in:

1- Calcification more frequent
2- Vasculitis ← skin, muscle, GIT (Ulceration, Hematemesis)
3- Low grade fever → Common
4- Hypertrichosis + lipoatrophy (Rare)
5- Malignancy (Rare)

→ **Associations**:

DM/PM & Malignancy
(paraneoplastic)
- lung cancer + GIT (most in men)
- Ovarian - Breast (most in women)
- Malignancy precede DM → 34%. Develop after it → 40%. occur together → 26%.

DM/PM & CTD (overlap S)
e.g: CREST, MCTD, SLE, Scleroderma, Sjogran S

Female : male
DM 4 : 1
& PM more than DM

- Histopathology:

- **Cutaneous lesions**:
  - as SLE → Flattening Epidermis
    → Hydropic Degeneration of Basal layer
    → edema of upper Dermis
    → perivascular lymphocytic infiltrate in upper Dermis
- **Muscle lesions**:
  proximal muscle → various Degree of Degeneration

- DIF: Globular deposits of IgM - IgG - C_3 in upper Dermis

- Lab Finding:

1. Urine: Albuminuria - Hematuria - Urinary Creatine
2. ↑ESR:
3. ↑ Serum Muscle enzymes: < CK, aldolase
   - ↑SGOT, alanine aminotransferase (ALT)
   - Lactic Dehydrogenase (LDH)
   - Myoglobin → Can detected in serum
4. Abnormal EMG:
5. Auto antibodies;

- non-myositis specific Abs
  - ANA Low titer
  - ANA High titr in overlap syndrome > 1:160
- Myositis-specific Abs
  - anti RNP (PM + SLE)
  - anti PM-Scl (DM-PM + Scleroderma)
  - Abs against MAS
  - anti-aminoacyl-tRNA synthetase (anti Jo-1)
  - Abs against Cytoplasmic protiens (anti-SRP)
  - Abs against Mi-2

- Diagnostic Criteria of PM/DM:

1- Proximal Symmetric Progressive Muscle weakness
(↓ weeks to months)

2- ↑CPK - aldolase - SGOT - SGPT - LDH

3. Muscle Biobsy : Inflamatory Myopathy

4- Electromyogram : Myopathy

5- Typical Cutaneous lesions of DM

Definite	probable	possible
4	3	2

(including Rash in DM) مهم جدا

- Poor prognostic Factors in DM:

- Progressive
- Old age
- initiating therapy after 24 months of muscle weakness
- Longer Duration of symptoms Befor Diagnosis
  - ↳ Pulmonary problems
  - ↳ Dysphagia
  - ↳ extensive Cutaneous lesion on Trunk
- ↳ Malignancy
- ↳ Cardiac issues

- treatment:

هنبتدي بيه ⊛ Systemic ⊛

1- * Oral predinsone : (1 mg/kg)
- tapered to 50% → over 6 months
- tapered to Zero → over 2-3 years
- Can use pulse Dose - Split Dose - alternate-Day

2- * Methotrexate : (5 - 20 mg/week)

3- * Azathioprine : (2 - 3 mg/Kg/Day)

* Others:

4 - IVIg : High Dose (2g/kg/Month)

5 - Cyclophosphamide : (0.5 - 1.0 g/m² month)

6 - Chlorambucil : (4 mg/Day)

7 - Cyclosporine : (3 - 5 mg/Kg/Day)

8 - Tacrolimus : (0.12 mg/Kg/Day)

9 - Mycophenolate mofetil

10 - Infliximab (5 - 10 mg/Kg/every 2 wks)

11 - Rituximab

12 - plasmapheresis

Cutaneous Lesion

1- Sun Screen
2- Topical Corticosteroids
3- Hydroxychloroquine
(200 mg Bid)
C↑ frequency of Drug eruption & DM)
4- Hydroxychoroquine + Quinacrine
5- Methotrexate
(Low Dose weekly 5-15 mg/wk)
6- Retinoids
7- Topical Tacrolimus
8- Calcinosis Cutis:
→ Diltiozem
→ Surgical excision
9- others:
- Mycophenolate Mofetil
- Dapsone
- Thalidomide
- Leflunomide
- Antiestrogens ← tamoxifen, anastrazole
- TNF-α inhibitors ← Infliximab, etanicept
- Rituximab

باختصار

	Skin involve		Systemic involve
LE →	DLE	ACLE	LE Nephritis without Cut. lesion LE
DM →	Amyopathic DM	classic DM	polymyositis/inclusion Body Myositis
SCL →	morphea, linear Scleroderma	systemic sclerosis	Systemic sclerosis Sine Scleroderma

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MCTD

→ HLA-DR4
→ HLA-DR2

- clinically:
  - → Raynaud's phenomenon → 100%
  - → Sclerodactyly → 90%
  - → arthralgia → 90%
- Rare systemic:
  - → esophgeal Dysmotility
  - → pulmonary fibrosis → Renal affection
- good prognosis & Long peiod of remission
- DIF: Epidermal nuclear IgG deposition
- IIF: speckled pattern
- Serology:
  - U1 RNP → High titers of Abs to ribonudeoprot
    - → Sensitive to ribonuclease
    - → 25% of ptn & SLE → Resistant to ribonuclease
  - -ve anti-n-DNA Abs
  - -ve anti-Sm Abs
- tt: prednisone 1 mg/kg/day, topical Steroids

Antiphospholipid syndrome

- **D.F:** multiple System Disorders
  Ch.ch By: ↑ APAs
  - arterial - venous Thrombosis
  - Thrombocytopenia
  - Recurrent Spontenous abortion
- **APAs:** Heterogenous group of circulating autoantibodies Directed against -Ve charged phospholipids
- **Autoantibodies include:**
  1- anticardiolipin
  2- lupus anticoagulant
  3- Anti-B2 glycoprotein-1 Abs

  ↓
  These antibodies Don't Bind to phospholidids themselves But Bind to protiens that Bind To phospholipids
  - Cardiolipin
  - phosphatidylserine

- **preliminary criteria for AS:**

Clinical criteria:
- Vascular Thrombosis (one or more epsiods)
- Complication of pregnancy
  - one or more unexplained Deaths of normal fetus after 10 wks
  - one or more premature Births of nomal neonate Before 34 wks
  - 3 or more unexplained consecutive spontaneous abortions Before 10th wk of gestation

(1 clinical + 1 lab)

Laboratory criteria
- Anticardiolipin Abs - IgG, IgM → at moderate or High level on one or more occasions at least 12 wks apart
- Lupus anticogulants Abs 2 or more occasions at least 12 wks apaits
- Anti-B2 glycoprotein-1 Abs ; IgG, IgM : 2 or more occasion at least 12 wks apart

- **Cutaneous manifistations of AS:** (livedo reticularis)

1- Livedo reticularis
2- Acrocyanosis
3- Necrosis
4- Nodules
5- Ulceration
6- Capillarities
7- Splinter Hge
8- Hemorrhage
9- Digital Ischemia/gangrene
10- Raynaud's phenamenon
11- Blue toe
12- Porcelain white Scars
13- Purpuric Cyanotic Macules

• Causes of 2ry AS:

↳ **Autoimmune Disease:**

1-SLE 4-PM/DM
2-RA 5-SJOgran$
3-SS 6-Myathenia gravis

↳ **Vascutis Disease:**

1. Temporal aiteriti's
2- Behcet Disease
3. Takayasu's Disease

↳ **Infection:**

Bacterial: TB, Syphilis, leprosy
Viral: HIV, Hepatiti's - IM
Protozoal: phemocystitis Carinii

↳ **Malignancy:**

- leukemia - paraprotinemia

↳ **Hematologic:**

- TTP - preincious anemia
- polycythemia vera

↳ **Drug associated:**

- Hydralazine - Quinidine
- phenytoin - interferon
- Chloropromazine

↳ **Dialysis in Renal Failure**

• Mechanism of Action of APAs:

1- APAs → Bind to → phospholipid Binding plasma Protiens

Causing →
- ∘ interferance è production + Relase of **Prostacyclin**
- ∘ interferance è **protien C + S** pathways
- ∘ **Activation** of platelats By interaction è platelat membrane phospholipids [33]
  - ∘ interferance è **Antithrombin III activity**
  - interefarance è **prekallikrein** activation to **kallikrein**
  - interferance è **Endothelial plasminogen** Relase
  - interferance è possible protective functions of Protiens as: B_2 glycoprotien-I, annexin V

• Catastrophic AP syndrome:

- Multi-Organ failure (Renal + Respiratory)
- Precipitated By:
  - Surgical procedures
  - Drugs (sulfur containing Diuretics - Captopril - OCPs)
  - Discontinue of anticoagulant Therapy
  - infection

• Histopathology: Non-inflammatory Thrombosis < arteries / veins

• Treatment:

1- Full anticoagulation → long term < 1ry / 2ry APS [warafin, Heparin]
+ Anti-Platelates agents
Mainstay of tt

2- Systemic Corticosteroids + immunosuppressives 2ry APS

3- Fibrinolytics, Plasma pheresis, Hydroxychloroquines, IVIg

other CTDs

Relapsing polychondritis

- **D.F:** Uncommon Inflammatory disorder Autoimmune origin affect Cartilage
- **Abs:** - Anti-Type II Collagen <50%
  ± anti-matrillin-1
- **Affected Cartilage:**
  - episodes of painful-Beefy Red Erythema
  - edema of Cartilagenous part of Ears
  - è time → Cartilage Destroyed
    [Cauliflower-floppy ears]
  - Nasal chondritis [saddle nose]
  - Respiratory involve [hoarseness]
  - migratory Arthralgia.
  - ↓ Hearing [deafness-tinnitus]
  - Ocular $
  - Associated è → Behcet $
    → myelodysplastic $
- **association:** HLA-DR4
- **Histology:** perichondrial inflammation è Neutrophils, plasma cells, lymphocytes
- **Tt:** Oral Corticosteroids - MTX
  Dapsone - Azathioprine

Sjogren's Syndrome

- **D.F:** Autoimmune Disorder affect mainly Secretory glands and Lacrimal, salivary gland
- **associated è:** HLA-B8, HLA DR3-HLA-DQ2
- **clinical:**
  - most Common :- ← Xerostomia, Xeropthalmia, arthritis
  - Cut manifestation :-
    - Xerosis - Petechiae - purpura ← palpable / nonpalbable.
    - Urticarial Vasculitis - Annular Erythema
- **Complications:**
  1- extranodal lymphoma
  2- peripheral neuropathy
  3- Hearing Loss
- **Labs:** ↑ESR
  +Ve → RF, anti-fodrin, anti-RO, anti-La
  Leukopenia
- **Histology:**  Dense lymphocytic infiltrate → Surround Salivary glands
- **treatment:** Mainly: Supportive
  - artificial tears
  - Cyclosporine eye Drops
  - methylCellulose Drops (artificial Saliva)

تجميعات

✱ wt is :

Magic Syndrome :
- Mouth + genital ulcers
- è inflammed Cartilage
- MAGIC
- antibodies to type II collagen
- Hx as Relapsing polychondritis

Schirmer test :
- piece of "whatman paper wick" folded over Lower eyelid
- For 5 minutes
- → if aqueous level of tear film migrate < 5 mm → Lacrimal gland Dysfunction

Cutaneous manifestations of Rheumatoid arthritis :
1. Rheumatoid Nodules : - S.C firm, over extensor surfaces area of Trauma or pressure
2. Pyoderma gangrenosum :
3. Small - medium sized vessel Vasculitis
4. Rheumatoid neutrophilic Dermatitis
5. Palisaded neutrophilic + granulomatous Dermatitis

Red Face :
- Connective Tissue : SLE, DM
- lymphoma
- Rosacea
- Dermatitis
- Flushing
- porphyria

+ve ANA :
- SLE and other CTD
- Phototherapy
- vascular Disorder

paraneoplastic syndrome
- Dermatomyositis
- Bazex $
- Bowen $
- Bullous eruption
- Migratory erythema
- Erythroderma

periorbital :
- Dermatomyositis
- Amyloidosis
- Angioedema
- Atopic Dermatitis
- Hylainosis Cutis
- millia
- Molluscum
- Kaposi sarcoma

Nail manifestations :
- Scleroderma → pitrygium inversa
- Dermatomyositis → Periungual Telangiectasia
- alopecia areata → pitting . thickening
- lichen planus → Ridging, Striation - ptreygium
- psoriasis → pitting, oil Drops, onycholysis

Related to Renal Disease :
- SLE
- Scleroderma
- Iry systemic amyloidosis
- Neurofibromatosis
- Tuberous sclerosis

Skin Diseases of Breast - Nipple :
- Morphea
- nipple eczema
- paget's Disease
- psoriasis
- Candidiasis
- BCC
- Bowen's Disease.
- lupus mastitis
- lupus panniculitis

Hypopigmented Macules in Trunk :
- Morphea
- Scarring DLE
- Tuberculoid leprosy
- Tinea versicolor
- Nevus anaemicus
- Nevus depigmentus
- Tuberus sclerosis
- Albinism
- vitiligo
- lichen sclerosis et atrophicus

Antibodies :
- Anti ds DNA = Native DNA = lupus Nephritis
- Anti - RNP = MCTD
- Anti - Smith = SLE
- Anti - Histone = Drug induced
- Anti - Ro - anti La = SCLE, Neonatal LE
- Terminal aminopeptide procollagen Type 1 = Morphea
- Terminal aminopeptide procollagen Type 3 = MTX

تجميعات

Cicatricial alopecia :

Congenital	Infection	CTD	Tumor
aplasia Cuti's	Kerion	DLE	BCC
Epidemal nevi	Favus	DM	SCC
poro)keratosis	leprosy	Morphea	Metastasis
	HZ		
	leshmenia		

Malar Rash:

- Lupus Erythematosus
- Granuloma facial e
- Contact Dematiti
- Bloom's Syndrome
- Actinic prurigo

Scales:

- DLE → adherent
- PVC → cigarrate paper
- P. resaca → Collerate
- PLC → mica scale s
- Psoriasis → laminated silvery

Hydropic degeneration of Basal cell layers :-

- DM
- LP
- DLE
- LSA

Diseases healed By Scarring :-

- DLE
- Kerion
- EB
- LV
- Favus
- Ecthyma
- PCT

Ectropion:

- DLE
- lamellar ecthyosis
- lupus vulgaris

	DLE	SCLE
CP	- Well-defined erythematous, discoid plaques with adherent scales & follicular plugging. - Healing →white, atrophic, non-contractile scar, slightly raised or hyperpigmented borders - Scarring alopecia - Sun exposed areas - MM, nail, eye affection	- Prominent photosensitive cutaneous lesions, non-scarring, papulosquamous or annular polycyclic lesions - Healing → grey-white hypopigmentation - Diffuse non-scarring alopecia - Photosensitivity 50% - Above the waist
HP	1- Hyperkeratosis with keratotic plugging 2- Atrophy of s.malpighii 3- Hydropic degeneration of basal cell 4- Thickening of BM 5- Patchy perivascular/periadnexal lymphocytic infiltrate 6- Edema, VD, ESR, colloid bodies in dermis	1- Hyperkeratosis & inflammatory infiltrate are less prominent 2- Hydropic degeneration & edema are more pronounced than DLE
Lab	1- DIF: granular deposits of IgG at DEJ 2- ESR ↑ 3- Leucopenia ↑ 4- +ve ANA in few cases	1- DIF: +ve 60% 2- ANA: +ve 60-80% 3- Circulating immune complexes 4- Anti-Ro, Anti-La Ab
ttt	1- Avoid PF 2- Topical sunscreen & steroid 3- Intralesional steroid 4- systemic: antimalarial- steroid Retinoid- thalidoamide- apsone	1- Avoid PF 2- Topical sunscreen & steroid 3- Systemic: antimalarial- steroid Retinoid- thalidoamide- apsone

	Scleroderma	scleredema
	CT disease	Metabolic disease
Def	Multisystem disease may be localized to skin (cutaneous sclerosis) or affects internal organs	Rapidly progressive, non-pitting edema& induration of skin
Types	1- Localized (morphea) 2- Systemic (diffuse, limited)	1- Idiopathic 2- Diabetic
Site	Hand, face, trunk	Begins in face, extends to neck, trunk, extremities Sparing palm & sole
CP	Non-pitting edema in hand & feet can't be fully extended Face: edema & fibrosis	Non-pitting edema, indurated body, skin can't be wrinkled, mouth difficult to open
Raynaud's	+ve	-ve
Telangiectasia	+ve	-ve
Scl70	+ve	-ve
HP	Early: inflammatory infiltrate, collagen, mast cells Late: swollen collagen, fibroblast	Excessive dermal mucin, separated by swollen collagen fibers
Systemic affection	Common	Rare
ttt	Steroid Penicillamin PUVA Physiotherapy Plastic surgery	PUVA Cyclophosphamide Corticosteroid

	scleroderma	Pseudoscleroderma
Def	Multisystem disease may be localized to skin (cutaneous sclerosis) or affects internal organs	Diseases have scleroderma-like changes
Types or causes	1- Localized (morphea) 2- Systemic (diffuse, limited)	1- Genetic: proderia 2- Metabolic: PCT, amyloidosis 3- Paraneoplastic: carcinoid 4- GVHD 5- Acrodermatitis chronic atrophican 6- CT: SLE, DM, RA 7- Occupational & chemical: silicosis 8- Itrogenic: silica, isoniazide
Raynaud's	+ve SS	-ve
Sclerodactyly	+ve SS	-ve
Acral lesions	+ve	-ve
Symmetry	symmetrical	asymmetrical
Sclerosis of skin	Edematous, sclerotic	Papules & nodules
Systemic affection	+ve SS	-ve
ANA	+ve	-ve
Scl 70 & anticentromere	+ve SS	-ve
Borrelia	+ve morphea	-ve except ACA
ttt	Steroid Penicillamin PUVA Physiotherapy Plastic surgery	Of the cause

Q Connective tissue diseases:

1- Discoid LE
2- Clinical & histopathological criteria of DLE
3- Chronic DLE variants.
4- Histopathology of LE.
5- Management of DLE
6- Compare: DLE & SCLE.
7- SCLE
8- Major diagnostic criteria of SCLE.
9- Major & minor criteria of SLE.
10- Most important diagnostic tests for SLE
11- How to investigate lupus nephritis.
12- Neonatal LE.
13- Systemic sclerosis: etiopathogenesis, autoantibodies, DD
14- Cutaneous manifestations of dermatomyositis.
15- Nail changes in dermatomyositis.
16- Diagnosis & management of dermatomyositis
17- Serology of connective tissue diseases.
18- Raynaud's phenomenon.
19- Pathophysiology & management of mixed connective tissue disease.
20-Serology of mixed connective tissue disease
21- Major diagnostic criteria of mixed connective tissue disease

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